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Short-term exposure to air pollution: Associations with lung function and inflammatory markers in non-smoking, healthy adults

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ABSTRACT

Introduction: Air pollution impacts health by increasing mortality and the incidence of acute events in unhealthy individuals. In contrast, the acute effects of pollution in healthy individuals are less obvious. The present study was designed to evaluate the associations between short-term exposure to air pollution on one hand and lung function, and inflammatory markers on the other in middle-aged, non-smoking adults with no respiratory disease, in two urban areas in northern France.

Methods: A sample of 1506 non-smoking adults (aged from 40 to 65) with no respiratory disease was selected from the participants in the 2011–2013 cross-sectional *Enquête Littoral Souffle Air Biologie Environnement* (ELISABET) survey in two urban areas in the northern France. We evaluated the associations between (i) mean levels of particulate matter with aerodynamic diameter < 10 µm (PM_{10}), nitrogen dioxide (NO_2) and ozone (O_3) exposure on the day and the day before the study examination for each participant, and (ii) spirometry data and levels of inflammatory markers. Coefficients of multiple linear regression models were expressed (except for the forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio) as the percentage change [95% confidence interval] per 10 µg increment in each pollutant.

Results: Levels of PM_{10}, NO_2 and O_3 exposure were below or only close to the World Health Organization's recommended limits in our two study areas. An increment in NO_2 levels was significantly associated with a lower FEV1/FVC ratio (−0.38 [−0.64; −0.12]), a lower forced expiratory flow between 25% and 75% of FVC (FEF25–75%) (−1.70 [−3.15; −0.23]), and a lower forced expiratory flow measured at 75% of FVC (FEF75%) (−3.07 [−4.92; −1.18]). An increment in PM_{10} levels was associated with lower FEF75% (−1.41 [−2.79; −0.01]) and a non-significant elevation in serum levels of high-sensitivity C-reactive protein (+3.48 [−0.25; 7.36], $p = 0.07$). Lastly, an increment in O_3 levels was associated with a significantly higher blood eosinophil count (+2.41 [0.10; 4.77]) and a non-significant elevation in fractional exhaled nitric oxide (+2.93 [−0.16; 6.13], $p = 0.06$).

Conclusion: A short-term exposure to air pollution was associated with a subclinical decrement in distal lung function and increment in inflammatory markers in healthy inhabitants of two urban areas in France. If these exploratory results are confirmed, this could suggest that even moderate levels of air pollution could have an impact on respiratory health on the general population, and not solely on susceptible individuals.

1. Introduction

Ambient air pollution increase mortality and decrease life expectancy (WHO, 2014; Pascal et al., 2016). In addition, air pollution is associated with the incidence of acute events in non-healthy patients (e.g. those with chronic obstructive pulmonary disease) (Dominici et al., 2006; Faustini et al., 2013; Faustini et al., 2012; Gan et al., 2013). In contrast, the acute effects of air pollution on healthy individuals are less obvious because the main effects are subclinical. For example, Faustini et al. did not observe a significant association between short-

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term air pollution and increased mortality in non-COPD individuals (Faustini et al., 2012). In healthy individuals, the documented effects of chronic pollution on lung function have been small, and there is a lack of evidence of acute effects of pollution on respiratory function (Berend, 2016). Although the effect on healthy individuals may be weak, air pollution may still be a major issue, indeed, even small changes in a health-related parameter in a large, exposed population may have a considerable impact on public health (Rose, 1985; Schindler et al., 2001). Short-term effects of air pollution on lung function have been observed in some population-based studies (Alexeeff et al., 2007; Cakmak et al., 2011; Chang et al., 2012; Rice et al., 2013). However, none of these studies focused on individuals with no respiratory disease.

The primary objective of the present study was to estimate the associations between short-term exposure to air pollution on one hand and lung function and levels of inflammatory markers on the other in middle-aged, non-smoking adults with no respiratory disease. The study was performed in two urban areas in northern France.

2. Methods

2.1. Population

The study population comprised male and female participants (aged from 40 to 65) from the 2011–2013 cross-sectional *Enquête Littoral Souffle Air Biologie Environnement* (ELISABET) survey in northern France. All participants had lived in the same city or its surrounding urban area (either Lille or Dunkirk) for at least five years, and were recruited between January 2011 and November 2013 (Quach et al., 2015). The participants were selected from electoral rolls by random sampling, with stratification for gender, age and center (Lille or Dunkirk), and were contacted in random order – and a cluster sampling frame was used for cities with a small number of inhabitants in the Lille urban area – so that the distribution of demographic data is as homogeneous as possible throughout the study. Each selected participant received a letter asking him/her to contact the coordinating team and make an appointment for data collection. In the absence of a reply, the investigators sent out repeated reminders by mail and, when possible, by telephone. Data were collected at home or occasionally during a consultation in a healthcare establishment. In all cases, a trained, registered nurse administered a detailed questionnaire. Lung function tests (spirometry testing and measurements of the fractional exhaled nitric oxide (FENO)) were also performed, and a blood sample was collected during the same visit.

We excluded ELISABET survey participants lacking acceptable spirometry data or data on any of the covariates. In order to avoid confounding effects in the relationships between air pollution, lung function and inflammatory markers, we also excluded participants fulfilling at least one of the following criteria: (i) self-reported chronic or acute respiratory disease or use of pulmonary medication, (ii) an airway obstruction (as measured by spirometry testing), (iii) exposure to active or passive smoking, and (iv) an inflammatory syndrome (as defined by a serum C-reactive protein (CRP) level > 10 mg/L).

The study protocol board (ClinicalTrials.gov identifier: NCT02490553) was approved by the local investigational review (CPP Nord Ouest IV, Lille, France; reference: 2010-A00065-34), in compliance with the French legislation on biomedical research. All participants provided their written, informed consent to participation in the study.

2.2. Spirometry testing and inflammatory marker assays

Spirometry testing was performed using Micro 6000 spirometers (Medisoft, Sorinnes, Belgium), according to the 2005 European Respiratory Society/American Thoracic Society guidelines (Miller et al., 2005). The spirometers were calibrated weekly. For each participant, the spirometry test was repeated until three acceptable flow-volume curves were obtained, following the same guidelines. No bronchodilators were administered. The greatest values of the forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), and peak expiratory flow (PEF) were selected for our statistical analysis. We also measured the forced expiratory flow between 25% and 75% of FVC (FEF25–75%) and the forced expiratory flow measured at 75% of FVC (FEF75%) from the maneuver that had the highest sum of FEV1 and FVC. All the maximal expiratory flow–volume (MEFV) curves were validated by an experienced, specialist physician (JLE). Airway obstruction was defined by a FEV1/FVC ratio below the lower limit of normal (5th percentile), as calculated with the most recent reference equations from the Global Lung Initiative 2012 (Quanjer et al., 2012).

The FENO was measured with the validated NIOX MINO portable analyzer (Aerocrine AB, Solna, Sweden) (Alving et al., 2006) at a constant expiratory flow rate of 50 mL/s, as describe previously (Giovannelli et al., 2016). Briefly, the NIOX MINO analyzer can detect FENO values from 5 to 300 ppb. Values below the limit of detection (LOD) were imputed with a value of 3.5 (LOD/$\sqrt{2}$) ppb. Measurements of FENO in the Lille urban area were excluded from our analysis because of significant inter-investigator heterogeneity.

The blood eosinophil count (B-eos) was measured with an LH780 hematology analyzer (Beckman Coulter, Fullerton, CA). The serum concentration of high-sensitivity (hs) CRP was measured using a nephelometric assay (BN ProSpec System, Siemens) with a detection range of 0.17 to 10 mg/L. Values below the LOD were computed as 0.12 (LOD/$\sqrt{2}$) mg/L.

Lastly, the following covariates were recorded: age, gender, educational level (number of years spent in full-time education, including primary school), height, and body mass index (BMI). Tobacco exposure was self-reported as either a current smoker (i.e. at least one cigarette per day for the previous 12 months), passive smoker (i.e. a never smoker exposed to tobacco smoke for at least an hour a day), a former smoker or a never-smoker.

2.3. Study areas

Two urban areas in northern France (Lille and Dunkirk, including the main city and close suburbs) were studied. We checked that the characteristics of this two urban areas were consistent with the Aphekom guidelines, i.e. with homogeneous exposure of the whole study area to a given air pollutant on a given day (Pascal et al., 2011). In essence, this means that the majority of the population should live and work within the study area; no part of the area should be under the influence of a large, stationary source of pollutant that would cause marked heterogeneity in pollutant levels; the urban study area should not be broken up by any large non-urban areas, and there should be no large changes in topography that would modify pollutant dispersion and concentrations (Pascal et al., 2011). To better visualize and analyze the characteristics of the two urban areas, we used a web-based tool (source: www.geoportail.gouv.fr) to map the roads, level of urbanization, topography, and distribution of atmospheric pollution monitoring stations.

The Lille area is a dense urban area, with only a few non-urban zones between the three main cities (Lille, Roubaix and Tourcoing) and two other cities (Armentieres and Comines). The road/motorway network in this area is very dense (Supplemental fig. 1).

The Dunkirk area is a coastal urban area. There are two break-points in the urban development: one to the east (between Dunkirk and Bray-Dune) and one to the west, including a large industrial zone between Dunkirk and Gravelines. The prevailing winds are south-westerly; as a consequence, air pollution from the industrial area is mostly pushed out to sea (data not shown). The road and motorway network is also dense in this area (Supplemental fig. 2).